Discovery and Characterization of BHV-7000: A Novel Kv7.2/7.3 Activator for the Treatment of Epilepsy

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Kv7 Potassium Channels Exquisitely Regulate Neuronal Firing

Kv7.2/7.3 channels are low-threshold voltage-gated potassium channels expressed in the CNS that modulate neuronal excitability[1]

- Mutations in Kv7.2/7.3 channels lead to seizures or other epileptic syndromes
- Preclinical studies have shown that activating Kv7.2/7.3 hyperpolarizes RMP, increases AP threshold, and has potent anti-seizure effects
- Kv7.2/7.3 channels are a clinically validated drug target

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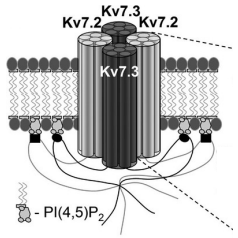

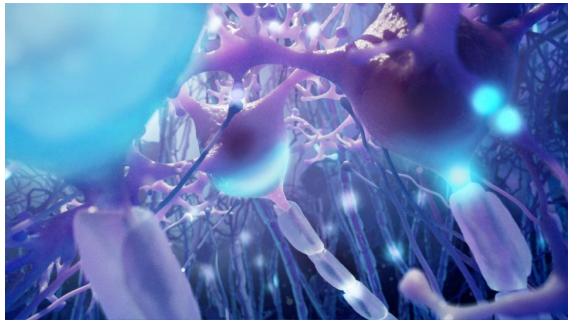

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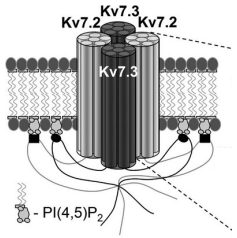

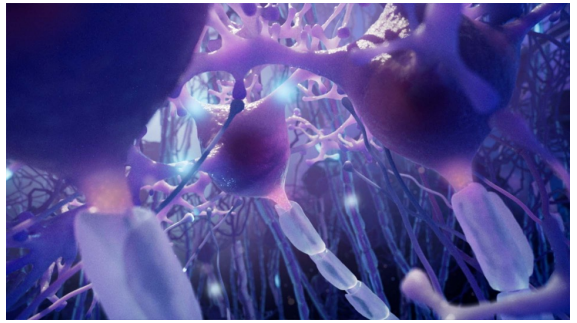

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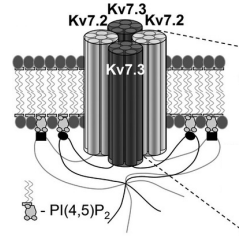

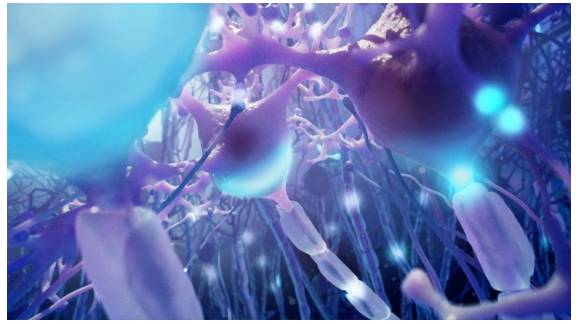

Precision targeting of Kv7 potassium channels may deliver robust efficacy while minimizing the risk of adverse effects associated with traditional anti-epileptic drugs

1. Vigil FA. *Front Physiol*. 2020;11:688. 2. Ventola CL. *P T*. 2014;39(11)776-792.

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Overview of Methods

- A screening tier was designed to discover potent and selective Kv7.2/7.3 activators
- Fluorescent and electrophysiological assays were employed to characterize lead compounds
- Antiseizure efficacy was evaluated in rats in the maximal electroshock seizure (MES) model and tolerability was assessed by neurological score (NS)
- Standard ADME and toxicology assays, including assessment of brain drug levels, were used to progress a candidate to the clinic
- A first-in-human phase 1 single ascending dose / multiple ascending dose (SAD/MAD) study assessed safety, tolerability, and pharmacokinetics in healthy subjects

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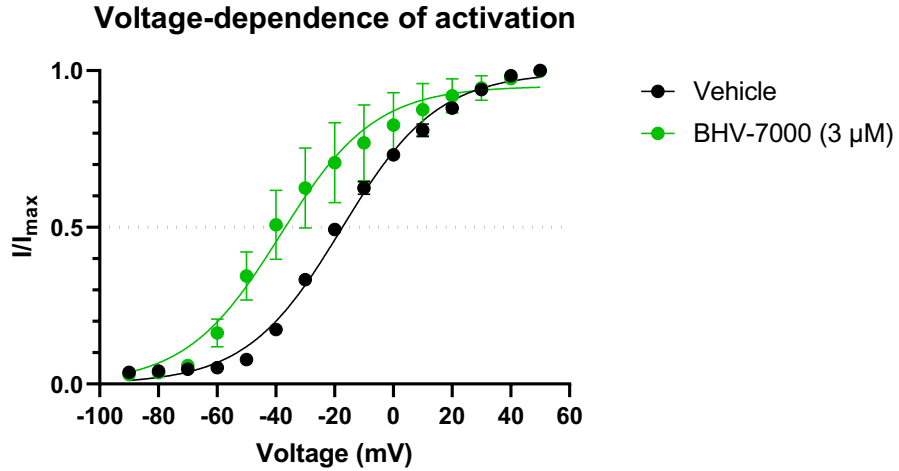
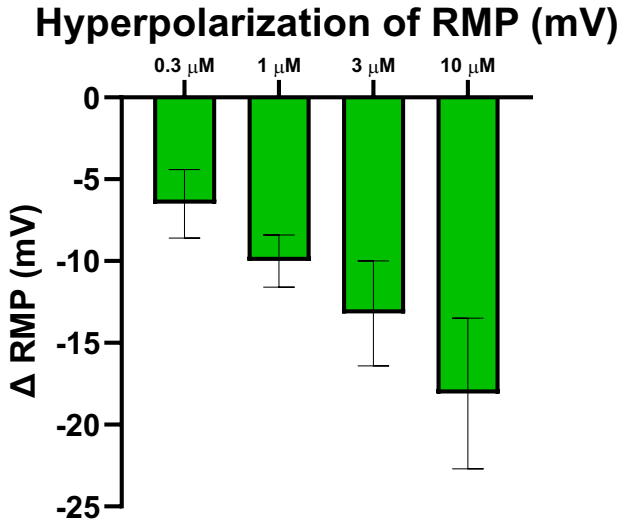
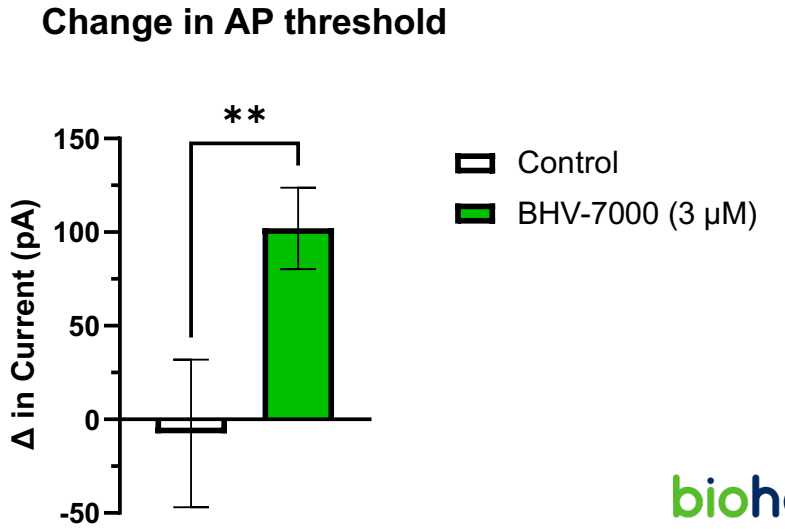
Effects of BHV-7000 on $V_{1/2}$, RMP, and AP threshold



Voltage-dependence of activation			
	0.3 µM	1.0 µM	3.0 µM
$V_{1/2}$ shift	-7.60	-15.21	-20.97





**P<0.01

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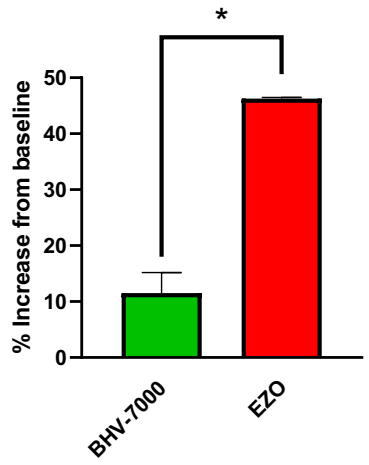
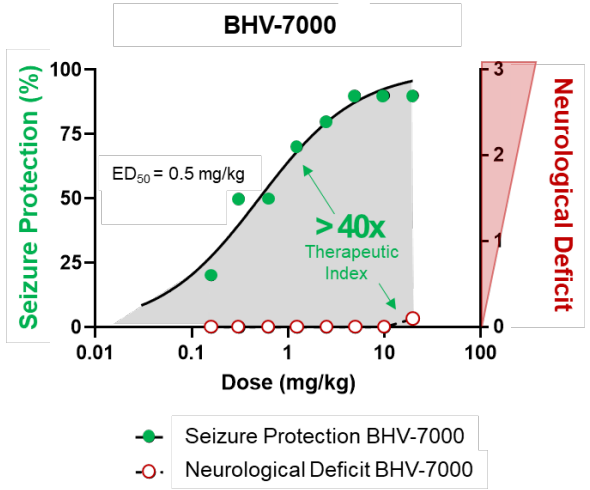
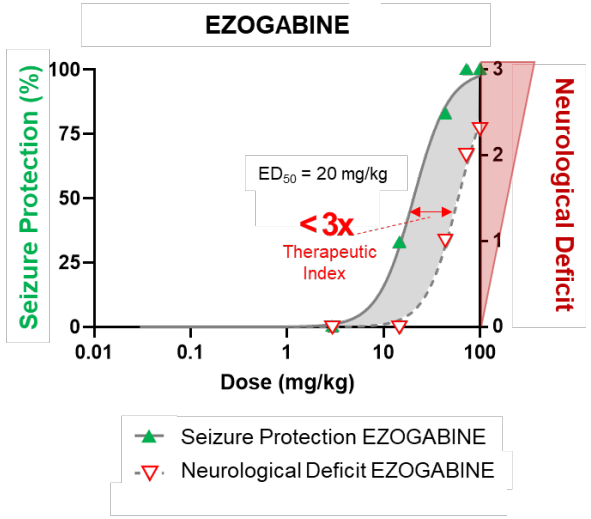
BHV-7000: Delivering potent anti-seizure effects with a wide tolerability index in the rat MES model



$GABA_A$ receptor activation

Purposefully dialed-out $GABA_A$ positive allosteric modulation





Targeted Kv7 activation enables seizure protection without impacting neurobehavior

*P<0.05

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BHV-7000 Phase I SAD/MAD Study: Well-tolerated without typical CNS adverse events seen with anti-seizure medications

Safety

- Single doses up to 100 mg and multiple doses up to 40 mg daily x15 days generally well-tolerated
- Most AEs mild and resolved spontaneously
- No serious or severe AEs
- No dose-limiting toxicities

Pharmacokinetics

- Target plasma concentrations for efficacy exceeded based on preclinical MES model
- High-fat meal had no effect on exposures

Adverse Event*	BHV-7000 MAD pooled (n=17)
Somnolence	0%
Headache	18%
Balance disorder	0%
Dizziness	0%
Memory impairment	0%
Sensory disturbance	0%
Speech disorder	0%

*MedDRA® Preferred Term within the System Organ Class of "Nervous System Disorders".
AE, adverse event; MAD, multiple ascending dose; MES, maximal electroshock seizure; SAD, single ascending dose

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Conclusions

- BHV-7000 is a novel and differentiated activator of Kv7.2/7.3 channels
- BHV-7000 is structurally and pharmacologically distinct from ezogabine
- BVH-7000 “dials-out” $GABA_A$ receptor activation
- BHV-7000 is potent in the MES epilepsy model without impact on neurobehavior
- BHV-7000 was well-tolerated in Phase 1 SAD/MAD studies without CNS adverse effects typical of anti-seizure medications

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Thank You!

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